



Supramolecular Synthons as Related to Cooperativity in Biocomplexes: towards Design and Development of Oligopeptide-Based Modern Drugs and Cosmeceuticals



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Abstract

Short oligopeptides of natural and synthetic origin are becoming increasingly important not only in research and modern drugs development but also as cosmeceuticals. On the other hand, complexes of proteins with peptide ligands have attracted wide attention in biomedicine. In particular, *in silico* and *in vivo* drug development is concerned. Therefore, detailed knowledge on supramolecular and energetic aspects of protein-peptide weak non-covalent interactions and their systematic evaluation is essential. In this mini review, we shed light into increasing potential of supramolecular synthon approach when cooperative effects in stabilization of biomolecules are to be concerned. We put forward the views on interpretation of protein-peptide ligand binding modes and the future development of innovative APIs.

Keywords: Oligopeptide-based Drugs; Cosmeceuticals; Supramolecular Synthon; Protein-ligand Biocomplex; Cooperativity; Anticancer therapy, Immunology; Drug delivery

Abbreviations: SMBBs: Simple Molecular Building Blocks; APIs: Active Pharmaceutical Ingredients; CSD: Cambridge Structural Database; PDB: Protein Data Bank; lp: Lone Pair

Introduction

Modern, first-in-class APIs designing, and development becomes a priority objective among scientists from various fields. Some of key issues in this context are being discussed briefly.

Discussion

Peptide-based drugs: "back to the future"

Peptides, as drugs, evolution started with the penicillin discovery around a century ago (in 1928). There is no doubt that it changed the course of medicine. In recent years, peptide-based therapies have a significant renaissance of interest. The progress is visible in the number of peptide drugs approved [1]. Moreover, it has been extended in relation to cosmeceuticals only recently [2]. Notably, definition of cosmeceutical was introduced by Dr. Kligman for agents on the borderline of cosmetics and drugs, delivering a biological activity in support of cosmetic action [3]. Simple molecular building blocks (SMBBs), i.e. amino acids and oligopeptides (consisting of 2-20 amino acids), have gained an growing attention due to their numerous advantages (ease of

large-scale synthesis, administration simplicity and superior properties: good stability, robustness, biocompatibility, natural availability, selective mode of action and low incidence of side effect, their easy modification for various purposes, i.e. chemical modification improves transdermal delivery of peptides, while cyclization enhances the affinity and selectivity) and applications (in anticancer therapy, immunology, drug delivery and so on) [4,5].

SMBBs, in biological systems, which architecture is controlled by non-covalent interactions, contain important structural information and make a valuable input in understanding biological systems and processes of complex topology.

Quality by design: supramolecular synthon idea targeting biocomplexes

Quality is a key to success in first-in-class drugs. It would be worth mentioning that quality of drug should be created right from the start, by precise designing. Therefore, rational design

of new, effective APIs (including multicomponent co-crystals, containing more than one active substance, like entresto - modern drug for chronic heart failure) should be based on the thorough knowledge of weak interactions at both molecular and higher topological levels. Nevertheless, the detailed information on this subject is still challenging. We would like to emphasize the importance of “a new old” concept of supramolecular synthons, recurring patterns of non-covalent interactions between functional groups [6-8], as related to biomolecules. This strategy is popular in supramolecular crystallography and crystal engineering.

It is manifested in the exploding number of publications. However, this idea is evolving in various fields and awaits for a new discovery in the nearest future [9]. We highlight its potential in study of biocomplexes. Intermolecular interactions form unique H-bond synthons between the corresponding main/side chain of protein and various scaffolds in ligands in the binding (active) site. The existence of synthons in protein-ligand complexes, in the context of synthons involving ligand water molecules, and also synthons formed by ligand-protein interactions in kinase sub-families in the active sites, has been noticed earlier by Sarhel [10] & Panigrahi [11], respectively. Nonetheless, synthons created only by classical H-bonds such as O (N, C)-H...O and N(C)-H...N were considered.

Supramolecular cooperativity: “what else?”

‘If the unfolded polypeptide from the ribosome had to sample all possible conformations to fold into a protein, it would take longer than the age of the universe’ should be in italics - ‘via’ should be in italics’ by quoting Levinthal [12]. In fact, this process takes milliseconds due to the cooperative interactions. In biological systems, numerous supramolecular interactions are observed. Cooperativity of weak intermolecular interactions plays a vital role in formation and defining the supramolecular synthons. An understanding of this issue is invaluable not only in modern APIs design but also in interpretation of priority biological phenomena, i.e. molecular recognition, supramolecular self-assembly or knowing behavior of biological and synthetic systems as well.

Indeed, cooperativity has different meanings in various fields. Historically, the chain configuration of three water molecules linked together via the H-bonds sequence has a stronger effect than two waters revealing cooperativity effect [12]. In other words, cooperativity is an increase of the interaction’s strength in the supramolecular aggregate when two or more intercontacts are formed among the neighbouring species [13,14].

Perspective

Oligopeptides bridge the gap between small molecules and macromolecules in novel drugs design and development. We focus on investigations of cooperativity of weak interactions (i.e. those involving aromatic rings such as CH... π / π ... π /cation... π /anion... π or a lone pair (lp)... π) in biocomplexes, keeping in

mind new biologically important supramolecular synthons [5], including a *Long Range Synthon Aufbau Modules* (LSAMs) [15,16]. As a prelude to description of biosystems, our recommendation is to introduce foundations for new direction of biocomplexes study, concentrating on quantitative aspects of cooperativity in the context of supramolecular synthons. Our own research, *via* modern experimental and *in silico* studies, we have been combined with information from the databases (CSD/PDB), which collect all secrets of molecular bio-crystals and provide a big data sets concerning diverse types of interactions. CSD-derived information, including SMBBs, is directly transferable and applicable to the protein environment.

Small molecules and proteins have natural synergy. Notably, quality of the 3D macromolecular crystal structures is getting better upon the time contain accurately determined geometries and consequently appropriate protein-ligand inter-contacts. More and more better models are available in the PDB thanks to modern, highly advanced crystallography. Preliminary studies are in progress and the results will be published in the future. Our findings will provide a valuable asset for understanding supramolecular multi-level architectures of SMBBs in combination with bio-systems. Significant advance in knowledge of bio-co-crystals engineering and supramolecular chemistry of biomolecules, which has a bright future ahead in advanced therapies including new generation complexed APIs, will be an additional consequence.

Conclusion

To summarize, the main message in this work is to emphasize the relevance of short peptides in development of next generation drugs and cosmeceuticals with improved therapeutic efficacy. And what is more, the supramolecular synthons idea can be a useful key for interpretation of the binding ligand-protein in biocomplexes and design innovative multicomponent peptide-based drugs. We hope that supramolecular insights into biocomplexes, and associated cooperativity, are of great value for the development of the life sciences providing a new outlook on interpretation of biological phenomena.

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